REMARKS

Claim 13 has been amended and new claims 32-37 added. The claim amendment and new claims find support throughout the application including the Drawings and claims as filed originally.

Claim 13 has been amended to point out explicitly what was implicit. Specifically, "derivative" language has been written with more precision. The claim also has language from claim 31 now canceled.

New claims 32-37 find specific support in the pending claims and those filed originally. The new claims encompass a specific invention embodiment in which the enzyme of SEQ ID NO. 2 is used in the method.

No new matter has been added by virtue of the claim amendment or new claims.

The Appeal Brief filed on December 1, 2003 ("Appeal Brief") is incorporated herein by reference.

35 USC §112, second paragraph (indefiniteness)

A. Claims 13 and 15-17 stand rejected as being indefinite under 35 USC §112, second paragraph. While Applicants must respectfully disagree with the position taken, basis for it has been addressed by this submission. In particular, claim 13 has been amended with language from claim 31 (reciting homology between particular fragments, derivatives and SEQ ID NO. 2.

Accordingly, reconsideration and withdrawal of this ground of rejection are respectfully requested.

B. Claims 13-17 and 31 stand rejected as being indefinite under 35 USC §112, second paragraph. While Applicants must respectfully disagree with the position taken, basis for it has

been addressed by this submission. In particular, preamble language from the independent claims has been amended to emphasize treatment applications of the claimed methods.

The present amendment of claim 13 (removing diagnosis-related language) should not be construed as an admission that the claimed methods could not be used to identify compounds for diagnosing a human neutral sphingomyelinase related disorder. The amendment is merely intended to further prosecution with the USPTO. The right to file subsequent applicants to this subject matter is reserved.

In view thereof, reconsideration and withdrawal of this ground of rejection are respectfully requested.

35 USC §112, first paragraph (enablement)

A. Claims 13, 15-17 and 31 stand rejected on grounds that the specification does not enable methods in which a particular fragment or a derivative of the human neutral sphingomyelinase is used. Although Applicant gratefully acknowledges that the Office deemed the specification enabling for use of the sequence represented by SEQ ID NO. 2, he must respectfully disagree that the disclosure is non-enabling for suitable fragments and derivatives of that sequence.

For instance, and as pointed out in the Appeal Brief, practice of the invention is not limited to any particular N-Smase so long as it can provide acceptable function. See eg., pg. 15, lines 25-29 ; pg. 16, lines 4-15; and pg. 17, lines 8-10 of the present application (disclosing particular invention methods in which suitable enzyme fragments or derivatives are used).

Specific examples of such acceptable N-Smases are disclosed throughout the present application. For example, pg. 7, lines 19-26 and Figures 1 and 2 of the present application disclose physical characteristics of the preferred native enzyme. Additionally suitable enzyme fragments or derivatives provide good activity in the standard activity gel assays as discussed eg., at pg. 8, lines 16-23 of the present application. Preferred activity ranges in the assay have also been provided. Moreover, N-Smase fragments or derivatives with particular amino acid

substitutions are disclosed at pg. 9, lines 1-20, for example. Nucleic acids that encode such suitable N-Smases are provided at pg. 10, lines 12-24 of the present application. Nucleic acids having preferred base pair sizes and N-Smases having desired functional domains are provided at pg. 10, line 12 to pg. 11, line 4 of the present application. Suitable enzyme isoforms are taught at pg. 11, lines 21-25 of the present application.

As understood, the rejection takes the position that notwithstanding Applicant's disclosure of many specific N-Smases suitable for use with the claimed invention, use of anything but the native enzyme is not enabled on grounds that it would require undue experimentation to make and use the N-Smases. Applicant cannot agree.

The present application provides examples of suitable N-Smases for use with the claimed invention including, but not limited to, the native enzyme. Should use of a particular enzyme fragment or derivative be needed in a specific invention embodiment, the specification provides more than ample guidance about selecting an appropriate fragment or derivative.

For example, preferred N-Smases including the native enzyme as well as fragments or derivatives thereof, exhibit good activity in the activity assay using ^{14}C-sphingomyelin and N-Smase peptide. See pg. 8, lines 16-23; and Example 6 of the present application.

Moreover, the chemical structure of the native N-Smase has disclosed both at the amino acid and nucleic acid levels. See Figures 1 and 2, for example. Important function domains in the structure are recognized. See pgs. 10-11 of the application, for example. Methods for producing suitable N-Smases, preferably by use of conventional recombinant means have been disclosed. See pg. 11, line 27 to pg. 12, line 10 of the application.

Accordingly, any testing needed to identify or confirm suitable N-Smases for use with the claimed invention is well within the level of experimentation permitted by the Federal Circuit. *In re Wands, 8* USPQ2d 1400 (Fed. *Cir. 1988).*

Applicant disagrees with the rejection on other grounds.

For example, a worker in this field would be able to use the guidance provided by the instant disclosure to select appropriate N-Smases. Any inoperable embodiments of the type described by the rejection could be readily avoided. As stated by the CPPA:

> [M]any patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit 'factors which must be presumed to be within the level of ordinary skill in the art.' ... There is nothing wrong with this so long as it would be obvious to one of skill in the art how to include these factors in such manner as to make the embodiment operative rather than inoperative. *In re Cook and Merigold,* 169 USPQ 299, 302 (C.C.P.A. 1971) (quoting *In re Skrivan,* 166 USPQ 85, 88 (C.C.P.A. 1970)).

Thus, one of skill having read Applicant's disclosure would know to identify suitable N-Smases in addition to the native enzyme. Even if one assumes for the sake of argument that a particular N-Smase fragment or derivative did not exhibit acceptable activity, that result, by itself, would not support the present enablement rejection. The worker would understand that another fragment or derivative as provided by the specification, could be tested and identified for suitable activity. The rejection has not provided any reason to doubt that the guidance provided by Applicant's disclosure could not be used to identify a range of acceptable N-Smases for use with the claimed methods.

It is noted that the rejection seems premised on the position that only claims drawn to exemplified invention embodiments satisfy the requirements of Section 112, first paragraph, notwithstanding the broader invention Appellant discloses.

Respectfully, such a position conflicts with established patent law. It is well-recognized that a patentee's invention is properly broader than specific embodiments identified in an application. Thus in *In re Anderson,* the CCPA reversed a rejection under Section 112, first paragraph and noted in particular (176 USPQ at 333):

> What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention. **This it may not do....** There is no doubt that a patentee's invention may be broader than the particular embodiment shown in his specification. A patentee is not only entitled to narrow claims directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. (emphasis added).

Here, the claimed invention is broader than use of the native N-Smase singled-out in the rejection. As taught throughout Appellant's disclosure, the invention is compatible with a variety of suitable N-Smases including specified fragments and derivatives thereof.

Finally, it is noted that the Office has acknowledged on the record the high level of knowledge in the art of enzymology. Such knowledge is presumed to include information about N-Smase as well as acceptable fragments and derivatives of that enzyme.

For such reasons, reversal of the final rejection under 35 U.S.C. 112, first paragraph is requested.

B. Claims 13 and 15-17 stand rejected as being non-enabled as provided at pgs. 7-8 of the Action. While Applicant disagrees with the rejection, it has been addressed. For instance, claim 13 has been amended with language from claim 31 now canceled.

35 USC §103-obviousness

Claims 13-17, and 31 stand rejected as obvious over Chatterjee et al. (JBC 264: 12554 (1989); Ogita et al. (WO 95/18119) and Ausbel et al. (Current Protocols in Mol. Biology, (1987); pgs. 10.03 to 10.06). Applicant respectfully traverses.

In response to remarks made in the Appeal Brief, the Office took the position that (Action at pg. 13):

> There is no need for the Examiner to provide references which disclose amino acid or nucleic acid sequences to support the rejection as the art has advanced so much that the availability of purified protein is enough for one skilled in the art to identify the nucleic acid encoding such protein and obtain recombinant protein.

Respectfully, the USPTO position is completely at odds with the record of this case. The argument is conclusory and provides no objective evidence that one could obtain amino acid sequences of the pending claims in view of the cited art. It is submitted that one of skill could certainly not obtain the nucleic acid encoding the featured protein absent the painstaking work performed by the inventor and his collaborators.

This is particularly true in view of the Declaration of Dr. Subroto Chatterjee (dated November 12, 2002) in which Dr. Chatterjee stated, among other things, that the USPTO position was not tenable with respect to the isolation of this particular enzyme. Specifically, he stated that it was not possible to make the recombinant N-Smase enzyme of claim 1 by using the approach outlined by the USPTO. Specifically, Dr. Chatterjee stated that it was not possible to obtain peptide sequence from the cited N-Smase enzyme and then use that sequence to make cloning probes. Declaration at ¶ 6-8.

However, and as stated by Dr. Chatterjee at ¶ 9-10 of the Declaration, he was able to make the recombinant N-Smase enzyme by using a protein expression cloning method. Use of that method according to Dr. Chatterjee required the isolation of a new antibody that was not taught or suggested from any of the cited references.

In the face of such compelling evidence that the recombinant N-Smase enzyme was indeed difficult to isolate and certainly not obvious from the cited references, the USPTO simply continues to disregard actual scientific evidence on grounds that Applicant should have been able to overcome his problems. Final Office Action at pgs. 9-10, bridging paragraph.

Respectfully, that is no basis for substantiating a rejection under §103 and it clearly does not constitute basis for maintaining the instant rejection. For instance, it ignores actual technical difficulties Applicant and skilled colleagues (from Harvard University) faced when they attempted to isolate the recombinant enzyme. Declaration at ¶6-8. None of these difficulties or a solution to them is taught or suggested by the references as relied on.

Applicant again notes that one alternative isolation method previously proposed by the Office (expression cloning) would require use of an antibody that recognizes the N-Smase enzyme. None of the cited references provides any specific teaching or suggestion about how to obtain or make such an antibody. Not surprisingly, the Office continues to remain silent as to where this antibody is to come from or whether a suitable antibody could be made at all. Indeed, it was the Appellant who discovered that it was possible to make a monospecific antibody against N-Smase and that the antibody could be used to isolate the recombinant enzyme. Declaration at ¶ 9-14.

At pgs. 13-14 of the Action, the Office took the position that "the art teaches various methods to make monospecific antibodies against any given protein". However, it is known that

isolation of certain antibodies are impossible or at least quite difficult. Nothing in the art cited by the Office teaches, suggest or provides any motivation to make an antibody that binds the subject enzyme.

The Office has indicated on the record that the obviousness rejection may be reconsidered if Applicant shows that the recombinant enzyme had unique properties which the natural enzyme of Chatterjee et al. does not. Applicant provided that evidence but in the present Action it is deemed unimportant.

In particular, the Supplemental Declaration of Dr. Subroto Chatterjee (dated May 28, 2003) stated various differences between the natural and recombinant enzymes. Such differences included the observation by the inventor that: (1) the natural enzyme had tightly associated proteases and phosphatases, and (2) recombinant N-Smase enzyme was more stable then the natural enzyme. It was thus noted by Applicant that the natural N-Smase enzyme cited by the Office has characteristics that are substantially different from the recombinant enzyme featured in Applicant's claim.

In the face of these unique properties, the Office has taken the position that (Action at pg. 14):

> None of these differences constitute a real structural/function difference between the purified and recombinant enzyme.

Applicants cannot agree. Dr. Chatterjee's Declaration clearly shows that the natural enzyme is different from the recombinant version by virtue of having an associated (and unwanted) protease activity. Moreover, the recombinant enzyme is more stable. A worker in this field would appreciate that the differences between the enzymes are real and substantial.

None of the cited references teach or suggest the foregoing problems associated with using the naturally-occurring N-Smase. Moreover, none of the cited references disclose or suggest Applicant's solution to these problems ie., making the recombinant N-Smase and using that enzyme instead of the natural enzyme in the claimed method.

Accordingly, reconsideration and withdrawal of the instant §103 rejection are respectfully requested.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Although it is not believed that any further fee is needed to consider this submission, the Office is hereby authorized to charge our deposit account **04-1105** should such fee be deemed necessary. The Office is expressly authorized to charge the account for any fee associated with entry of new claims 32-37.

Respectfully submitted,

Date: 10 August 2003

Robert L. Buchanan
Reg. No. 40,927
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205
Telephone: 617-439-4444
Fax: (617) 439-4170 / 7748

Customer No. 21874